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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,497	04/13/2004	Joseph Pontillo	690068.555C1	3284

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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,497	PONTILLO ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-12, drawn to compound of formula shown in claim1 wherein A = N, namely 2,3-dihydropyrazolo[3,2-c]pyrimidine-5,7-dione, composition and method of use, classified in class 544, subclass 281, class 514, subclass 258.

II. Claims 1-12, drawn to compound of formula shown in claim1 wherein A = O or S, namely 2,3-dihydroxazolo[3,2-c]pyrimidine-5,7-dione and ,3-dihydrothiazolo[3,2-c]pyrimidine-5,7-dione, composition and method of use, classified in class 544, subclass, subclass 278, class 514, subclass 258.

III. Claims 1-12, drawn to compound of formula shown in claim1 wherein A = OCR^7R^8, namely (1,3-oxazino)[3,2-c]pyrimidine-5,7-dione, composition and method of use, classified in class 544, subclass 91, class 514, subclass 230.5.

The inventions I, II and III are distinct, each from the other because of the following reasons:

Invention I, II and III are independent and distinct from each other because they are directed to structurally dissimilar compounds that lack common core namely pyrazolo[3,2-c]pyrimidine versus oxazolo[3,2-c]pyrimidine or thiazolo[3,2-c]pyrimidine

versus (1,3-oxazino)[3,2-c]pyrimidine. Consequently, the groups have different classifications and require separate prior art searches. They can be made and used independently. Art, which may render obvious or anticipate one of the groups would not necessarily do the same for the other group. Each can support a patent, as the compounds of each group are capable of being utilized alone not in combination with other members listed in the Markush group.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Karl Hermann on 9/27/2004 a provisional election was made with traverse to prosecute the invention of Group I claim1-12. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-12 will be examined to the extent they embrace the elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply. Any claim not specifically rejected is rejected as being dependent on a rejected claim.

1. In claim 1, recitation of the term "prodrug' is deemed as indefinite. Prodrugs in general and as noted in specification, page 20, are compounds, which undergo in vivo hydrolysis to parent active drugs. In that sense recitation of prodrug is acceptable. However, the definition of various R, groups include such groups, namely esters, amides, alkoxycarbonyl etc. and therefore it is not clear what is the difference between these variable groups and the prodrug groups. Applicants should note the ambiguity that if the variable groups are prodrug, which are in general inactive but becomes active upon in vivo transformation, then the compound bearing the variable group would be deemed as inactive which is not what the claim recites.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-10 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preventing pregnancy and treating prostate cancer, does not reasonably provide enablement for all or any sex-hormone related conditions and or antagonism of gonadotropin-releasing hormone receptor including those yet to be discovered as due to the said mode of action embraced in the claim language. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following reasons apply.

The instant claims are drawn to "treating a sex-hormone related condition" or "antagonism of gonadotropin-releasing hormone receptor". Note mode of action of the compound(s) is related to treating diseases as recited in the specification. The scope of the claims includes not only any or all conditions but also those condition yet to be discovered for which there is no enabling disclosure. In addition, the scope of these claims includes treatment of various diseases, which is not adequately enabled solely based on the gonadotropin-releasing hormone receptor antagonist binding activity of the compounds provided in the specification at pages 3-4 and 20-24.The instant compounds are disclosed to have gonadotropin-releasing hormone receptor antagonist activity and it is recited that the instant compounds are therefore useful in treating any or all sex-hormone related disorders, for which applicants provide no competent evidence. However, the applicants have not provided any competent evidence that the

instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the gonadotropin-releasing hormone receptor antagonist

activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Huirne, JA, and Lambalk, GB., (Lancet 358(9295): 1793-1803, 2001, PubMed Abstract provided), which suggest that current status at best exploratory and need further experimentation. Note method of use for assisted reproduction and treating prostate cancer is also taught therein.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating diseases that require gonadotropin-releasing hormone receptor antagonist receptor activity.

2) The state of the prior art: A very recent publication expressed that the gonadotropin-releasing hormone receptor antagonist effects are unpredictable and are still exploratory.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely

with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all condition and the state of the art is that the effects of gonadotropin-releasing hormone receptor antagonist are unpredictable and at best limited to assisted reproduction and treating prostate cancer.

6) The breadth of the claims: The instant claims embrace any or all condition including those yet to be related to sex-hormone related disorders.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of receptor-ligand interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Claims 8-10 and 12, although positively recite specific condition/disease, examiner could not find prior art support for these conditions/diseases. Applicants may

cite references to support the nexus between gonadotropin-releasing hormone receptor antagonist effects and the positively recited conditions/diseases of claims 8-10 and 12 to obviate the rejection of these claims.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making prodrugs of the claimed compounds. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry - to use the invention. "The factors to be considered in making an enablement rejection have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", In re Rainer, 146 USPQ 218 (1965); In re Colianni, 195 USPQ 150, Ex parte Formal, 230 USPQ 546. a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, and produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism 'de novo, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active.

Thus, determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is found in the passage spanning line 32, page 12 to line 11, page 13. c) There is no working example of a prodrug of a compound the formula (I). d) The nature of the invention is clinical use of compounds and the pharmacokinetic behavior of substances in the human body. e) The state of the prodrug art is summarized by Wolff (Medicinal Chemistry). The table on the left side of page 976 outlines the research program to be undertaken to. find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modem Pharmaceutics) in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug. I) Wolff (Medicinal Chemistry) in the last paragraph on page 975 describes the artisans making Applicants' prodrugs as a collaborative team of synthetic pharmaceutical chemists and metabolism experts. All would have a Ph. D. degree and several years of industrial experience. g) It is well established that "the scope of enablement varies inversely degree of unpredictability of the factors involved", 'and physiological activity is generally considered to be an unpredictable factor. See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula of claim I as

well as the presently unknown list potential prodrug derivatives embraced by the word "prodrug".

Thus, undue experimentation will be required to determine if any particular derivative is, in fact, a prodrug.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is Mukund Shah whose telephone number is (571) 272-0674. If Applicants are unable to reach Mukund Shah within 24-hour period, they may contact James O. Wilson, Acting-SPE of art unit 1624 at 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (703) 872-9306. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Venkataraman Balasubramanian

Venkataraman Balasubramanian

09/27/2004